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Editorial

Iron in Coronary Heart Disease—J-Shaped Associations and Ambivalent Relationships

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Iron exerts essential functions for human life, for example, in oxygen transport, ATP production, and DNA synthesis. However, iron overload also facilitates the production of potentially harmful reactive oxygen species. Iron homeostasis is predominantly regulated by intestinal adsorption as well as uptake, storage, and resecretion by macrophages and hepatocytes. The master-regulator hepcidin is mainly produced by the liver and suppresses the iron exporter ferroportin I. Hepcidin expression is low when iron is missing but increases upon iron overload or stimulation by inflammatory cytokines such as interleukin-6. As a consequence, iron release into the circulation from enterocytes, macrophages, or hepatocytes increases with iron deficiency but decreases with iron overload or inflammation. The latter condition leads to functional iron deficiency in inflammatory diseases *(1)*. For transport in the circulation and storage in hepatocytes and macrophages, iron is bound by transferrin (Tf)[2] and ferritin, respectively. The Tf receptor (TfR) mediates the uptake of the Tf/iron complex into cells. The expression of Tf and TfR is upregulated upon lack of iron. Some TfR is shed from the cell-surface and becomes detectable in plasma as soluble TfR (sTfR). Increased plasma concentrations of Tf and sTfR as well as a low concentration of ferritin are indicative of iron deficiency. The opposite is found in iron overload. However, in contrast to sTfR, Tf and ferritin are acute-phase reactants so that their plasma concentrations decrease and increase, respectively, in inflammatory states. For the assessment of iron status, therefore, ferritin, Tf, and hepcidin, as well as derived biomarkers such as Tf saturation (Tf-sat) and sTfR/ferritin ratios, must be interpreted in the context of C-reactive protein (CRP) *(1)*.

Both iron deficiency and iron overload have been associated with increased cardiovascular morbidity and mortality. The evidence is strongest for heart failure: Hemochromatosis leads to cardiomyopathy *(2)*. Iron deficiency has been associated with poor prognosis in heart failure patients even independently of anemia. Randomized controlled trials have demonstrated the beneficial effects of intravenous ferric carboxymaltose therapy in patients with heart failure with reduced ejection fraction (HFrEF). Indeed, current guidelines recommend the assessment of iron status in patients with newly diagnosed heart failure and treatment of HFrEF patients with ferritin <100 μg/L or ferritin of 100–299 μg/L and Tf-sat $<20\%$ with intravenous ferric carboxymaltose *(3)*.

The role of iron in atherosclerotic cardiovascular disease (ASCVD) and its complications is less obvious. Iron accumulates in atherosclerotic lesions. The earlier onset of ASCVD in males as compared to women and the disappearance of this female gender advantage after menopause have been suggested to reflect differences in iron exposure of men and premenopausal women. Regular blood donation was associated with reduced risk of ASCVD events and reduced all-cause mortality *(4)* Conversely, mortality was increased in patients who had an acute coronary syndrome (ACS) and received blood transfusions *(5)*. However, blood donors have a healthier lifestyle than nondonors and ACS patients receiving blood transfusions have comorbidities that limit life expectancy. Supporting a proatherogenic effect of iron overload, carriers of mutations in the hemochromatosis gene *HFE* were found to be at increased risk of ASCVD in some but not all studies *(4, 5)*. Previous epidemiological studies, which measured biomarkers of iron metabolism, yielded opposing evidence. Two meta-analyses of 32 and 17 studies involving more than 290 000 and 150 000 individuals, respectively, found inverse associations of Tf-sat or iron with coronary heart disease (CHD) events or mortality *(6, 7)*. In agreement with an adverse impact of iron deficiency on CHD, a recent Mendelian randomization study also found evidence for reduced risk in individuals with genetically determined higher concentrations of iron and ferritin as well as Tf-sat *(8)*.

In this issue of *Clinical Chemistry,* Grammer and colleagues mirror this controversy by a report on J-shaped associations of conventional biomarkers of iron load with both cardiovascular and total mortality of >2100 patients who underwent diagnostic coronary angiography and were followed up for nearly 10 years in the LUdwigshafen RIsk and Cardiovascular Health (LURIC) study

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[2] Nonstandard abbreviations: Tf, transferrin; TfR, transferrin receptor; sTfR, soluble transferrin receptor; Tf-sat, transferrin saturation; CRP, C-reactive protein; HFrEF, heart failure with reduced ejection fraction; ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; CHD, coronary heart disease; LURIC, LUdwigshafen RIsk and Cardiovascular Health.

(9). By visual inspection, the nadirs of spline curves for iron, Tf-sat, ferritin, sTfR, and sTfR/ferritin ratio were 1.15 mg/L, 32%, 250 μg/L, 1.15 mg/L, and 0.5, respectively. Only plasma concentrations of hepcidin showed a continuous and inverse association with both total and cardiovascular mortality. Also of note, after adjustment only for age and sex, hemoglobin concentration did not show any significant association with either total or cardiovascular mortality *(9)*.

After maximal multivariate adjustment for age, sex, cardiovascular risk factors, CRP, hemoglobin, and NT-proBNP (N-terminal fragment of B-type natriuretic propeptide), high sTfR and high sTfR/ferritin ratio reflected the strongest association of iron deficiency with total and cardiovascular mortality. Compared to the second quartiles as the reference, the hazard ratios of sTfR and sTfR/ferritin ratio in the highest quartiles were 1.76 (95% CI, 1.39–2.22) and 1.53 (95% CI, 1.22–1.92), respectively, for total mortality, and 1.76 (95% CI, 1.39–2.22) and 1.53 (95% CI, 1.22–1.92), respectively, for cardiovascular mortality. High iron concentrations and high Tf-sat were the strongest indicators of increased mortality risks associated with high iron status. Compared to the third quartiles as the reference, the hazard ratios of iron and Tf saturation in the fourth quartiles were 1.44 (95% CI, 1.10–1.87) and 1.37 (95% CI, 1.05–1.77), respectively, for total mortality, and 1.52 (95% CI, 1.08–2.14) and 1.54 (95% CI, 1.10–2.16), respectively, for cardiovascular mortality *(9)*.

The LURIC study advances our knowledge by the comprehensive analysis of iron status in a rather large cohort with high event rates and long-term follow-up *(9)*. Large sample sizes and event rates are needed to unravel the J-shaped associations. Most previous studies were too small or hid nonlinear associations by analyzing data in tertiles rather than by higher quantiles or continuously. However, several studies observed parabolic associations of CHD with biomarkers of iron metabolism or seemingly contradictory associations, for example, positive with ferritin but inverse with iron or Tf saturation *(4, 6)*. J-shaped associations of iron biomarkers have been reported in diabetic subjects *(10)*. Opposite associations of ferritin with mortality have been observed in men and women *(11)*. Similar subgroup analyses would be interesting to see in the LURIC study as well.

The LURIC study also went beyond other studies by analyzing the less widely investigated biomarkers sTfR and hepcidin. As yet, data on the prognostic role of these biomarkers in CHD are scarce and controversial. A recent study in diabetic patients found sTfR concentrations positively associated with cardiovascular mortality *(10)*. For hepcidin, all kinds of associations have been reported, positive, inverse, and not significant, but in much smaller studies as compared to LURIC *(12–14)*. The combination of high sTfR and low hepcidin has been termed systemic body iron release. Recently, this condition was encountered in nearly one third of patients with acute heart failure or CHD *(13, 15)*. Contrary to the findings of Grammer et al., who did not analyze this combination directly, Ruhe et al. found systemic body iron release to be associated with a significantly reduced risk of cardiovascular death [fully adjusted HR = 0.37 (95% CI, 0.14–0.99)] in 811 patients with angiographically determined stable CHD, which were followed up for 4 years *(13)*. However, in a study of 165 acute heart failure patients, the combination of low hepcidin and increased sTfR was associated with increased 12-month mortality *(15)*. The controversial findings, especially on hepcidin, may have biological and analytical explanations. Plasma concentrations of hepcidin not only reflect cellular iron content but are also confounded by inflammation and kidney and liver function, as well as metabolic diseases *(1, 4)*. Adjustments alleviate but do not abolish the impact of these confounders. Differences in kind and stage of disease, prevalence of comorbidities and treatments, duration of follow-up, and definitions of follow-up may have contributed to the different findings in different studies. Moreover, standardization of hepcidin and sTfR measurements have been initiated only recently *(1)*. However, Grammer et al. *(9)*, Ruhe et al. *(13)*, and Li et al. *(14)* used an ELISA from the same manufacturer.

What are the clinical consequences of the findings in the LURIC study? The authors are right not to encourage the measurement of iron status in CHD patients for several reasons. In general, the observed associations need to be confirmed by other large, well-characterized cohort studies in various settings (ACS, stable CHD, asymptomatic population) and endpoints (fatal and nonfatal ASCVD events, mortality, and specific causes of death). This is especially true for sTfR and hepcidin, which have been investigated in only a few, mostly small, studies with controversial results. Both from a diagnostic and a therapeutic perspective, substantial research efforts are needed to prove clinical utility of recording iron status in CHD patients: Does recording of iron status improve risk prediction over established clinical criteria and laboratory data, such as the pooled cohort equation in asymptomatic individuals or the TIMI or GRACE scores in symptomatic ASCVD patients? Does (intravenous?) iron supplementation or phlebotomy in CHD patients with iron-deficiency and iron-overload, respectively, prevent ASCVD events or prolong life expectancy?

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and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

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